UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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UNITED STATES OF AMERICA	**CRIMINAL NO.** 10-10431-MBB
v.	**VIOLATIONS:** Title 21 U.S.C. §§ 331(a), 333(a)(1) and 352(f)(1) (Introduction into Interstate Commerce of a Misbranded Drug).
ELAN PHARMACEUTICALS, INC.,	
Defendant.	

INFORMATION

The United States Attorney charges that:

GENERAL ALLEGATIONS

At all times material to this Information, unless otherwise alleged:

1. **ELAN PHARMACEUTICALS, INC.** ("**EPI**") was a Delaware corporation with its principal place of business in South San Francisco, California. **EPI** was a wholly owned subsidiary of Elan Corporation, plc ("Elan"), a publicly traded Irish corporation headquartered in Dublin, Ireland (NYSE ticker symbol: ELN). During the relevant time frame, **EPI** developed, marketed and sold pharmaceutical products in the United States.

2. From in or about May 2000 through April 2004, **EPI** marketed, promoted and sold Zonegran, an anti-epileptic drug ("AED"), including in the District of Massachusetts.

3. On or about April 28, 2004, **EPI** sold Zonegran, the drug's assets, the United States license to market and sell Zonegran, and the Zonegran sales force to another pharmaceutical company for approximately $128.5 million.

The FDA and the FDCA

4. The Food and Drug Administration ("FDA") was the federal agency of the United States responsible for protecting the health and safety of the public by enforcing the Federal Food Drug and Cosmetic Act ("FDCA"), 21 United States Code, Section 301, *et seq.* and ensuring, among other things, that drugs intended for use in humans were safe and effective for each of their intended uses and that the labeling of such drugs bore true, complete and accurate information.

5. The FDCA, and its implementing regulations, required that, with certain exceptions not relevant here, before a new drug could legally be introduced into interstate commerce, a sponsor of a new drug submit and obtain approval of an new drug application ("NDA") from the FDA.

6. The FDA required that the NDA include proposed labeling for the proposed intended uses of the drug which included, among other things, the conditions for therapeutic use. The NDA was also required to contain, to the satisfaction of the FDA, data generated in adequate and well-controlled trials that demonstrated that the drug would be safe and effective when used in accordance with the proposed labeling.

7. An NDA sponsor was not permitted to promote and market a new drug until it had an approved NDA, including approval for the proposed labeling. Moreover, if approved, the sponsor was permitted to promote and market the drug only for the medical conditions, uses and dosages specified in the approved labeling. Uses not approved by the FDA, including dosages not approved in the drug's labeling, were known as "unapproved" or "off-label" uses.

8. The FDCA, and its implementing regulations, required the sponsor to file a Supplemental NDA (or "sNDA"), in order to label or promote a drug for uses or dosages different from the conditions for uses and dosages specified in the approved labeling. The sNDA was required to include a description of the newly proposed indications for use, and evidence consisting of well-controlled clinical studies, sufficient to demonstrate that the drug was safe and effective for the newly proposed therapeutic use. Only upon FDA approval of the sNDA could the sponsor promote the drug for the new intended use.

9. The FDCA provided that a drug was misbranded if, among other things, its labeling did not contain adequate directions for use. 21 U.S.C. § 352(f)(1). As the phrase was used in the FDCA and its regulations, adequate directions for use could not be written for medical indications or uses for which the drug had not been approved and proven to be safe and effective through adequate and well-controlled clinical studies.

10. The FDCA prohibited the delivery for introduction and causing the delivery for introduction into interstate commerce of a misbranded drug. 21 U.S.C. §§ 331(a).

The Zonegran Approval Process

11. In or about March 1997, **EPI** acquired the license for Zonegran from a predecessor company which had filed the NDA for Zonegran with the FDA. In or about January 1999, **EPI** became the sponsor of the NDA.

12. On or about March 27, 2000, the FDA approved Zonegran for use as adjunctive therapy (combination therapy) in the treatment of partial seizures in adults over the age of 16 with epilepsy (the "approved use").

13. In its approval letter for Zonegran, the FDA expressly did not approve the use of

Zonegran in pediatric patients, and noted specifically that **EPI** had not fulfilled the required studies to gain approval for use in pediatric patients. At the same time, the FDA raised with **EPI** concerns about the safety of the use of Zonegran in children due to the incidence of potentially severe side effects, including but not limited to oligohidrosis (decreased sweating) and hyperthermia (overheating).

14. In response, **EPI** advised FDA that **EPI** would conduct Phase 4 (post-marketing) studies on the pediatric use of Zonegran. However, in or about July 2003, **EPI** made a "business decision" to discontinue those studies but did not notify FDA of this decision until mid-August 2003. **EPI** never submitted data to the FDA to demonstrate the safety and efficacy of Zonegran for use in children, and the FDA never approved Zonegran for pediatric use.

15. On or about April 19, 2000, **EPI** submitted an sNDA to the FDA seeking approval of two lower dosage strengths of Zonegran, 25 mg and 50 mg. On August 22, 2003, **EPI** received FDA approval for these two lower dosages of Zonegran. Thereafter, **EPI** marketed these lower dosages of Zonegran as "flexible dosing options" to increase sales of Zonegran for unapproved uses, including use in children and in patients who suffered migraine headaches.

16. From in or about March 2000 through in or about August 2001, **EPI** advised the FDA that it would conduct Phase 4 clinical studies on Zonegran concerning the safety and efficacy of Zonegran in monotherapy (use alone) and not in combination therapy. **EPI** never submitted an sNDA for the use of Zonegran in monotherapy and the FDA never approved such use.

17. In or about April 2001, **EPI** analyzed the return on investment of conducting further clinical trials to obtain FDA approval for additional uses of Zonegran, and explicitly

considered the expense of conducting the trials, the time needed to complete the trials, and the pending expiration of the Zonegran patent in March 2005. Over time, **EPI** made a series of business decisions not to seek FDA approval for any use of Zonegran beyond the approved use or additional doses beyond the lower doses of 25 and 50 mgs.

18. The FDA never approved Zonegran for any use other than the approved use, and in particular, never approved the use of Zonegran for children; monotherapy; neuropathic pain; migraines or chronic daily headaches; obesity or weight loss; eating disorders such as binge eating, bulimia nervosa and anorexia; psychiatric disorders including mania and bipolar; and movement disorders such as Parkinson's Disease (collectively, the "unapproved uses").

The Limited Market for Zonegran

19. When **EPI** launched Zonegran in May 2000, the drug was the last of three new AEDs introduced to the market in 2000, and the last of seven AEDs on the market at that time. The other AEDs had broader approvals from the FDA than Zonegran. Zonegran faced a steep uphill battle to obtain sales and, during its first year, Zonegran's market share ranged between 0.22% and 1.0%.

20. In 2002, **EPI** came under significant financial pressure as a result of, among other factors, an investigation into **EPI's** financial practices by the Securities and Exchange Commission, during which **EPI**'s stock prices dropped from a high of $65 per share to $2 per share in six months. As a result, **EPI** evaluated various means to raise cash, including which drugs to divest and which drugs to retain because of potential profit. As part of that evaluation, **EPI** conducted market research and decided to retain Zonegran because of its large potential for growth, particularly in unapproved uses.

Sales Campaigns Designed to Obtain Off-Label Sales

21. In response to its financial difficulties, **EPI** developed a series of promotional sales campaigns to obtain additional revenues through sales of Zonegran for unapproved uses:

A. ***Expect More***. In or about April 2002, **EPI** launched a promotional campaign for Zonegran entitled, "***Expect More, Expect Zonegran***," that included the direction to the sales force to:

* "**Expect More than adjunctive therapy for partial seizures**. *Sell MOAs [mechanisms of action]– allows physician to think beyond just partial seizures."*
* "**Expect more than just use in epilepsy.** *Opens doors for psychiatry, pain, headache, etc."*

The sales aid for the campaign included a diagram that highlighted Zonegran's "Multiple Mechanisms of Action" which related primarily to unapproved uses for Zonegran in psychiatric disorders, movement disorders, obesity or weight loss, pain management and headaches.

B. ***Demand More***. In or about December 2002, **EPI** introduced the "**Demand More**" promotional campaign which included a sales aid that depicted a group of young adults holding hands, climbing a mountain, and a graphic diagram that highlighted Zonegran's "multiple and complementary mechanisms of action." This sales aid included, among other claims, misleading information such as (i) a comparison chart of the potential mechanisms of action of Zonegran with that of its competitor drugs, noting that only Zonegran covered each of the highlighted characteristics, a chart which was not based upon any head-to-head clinical trials; and (ii) the misleading claim that "Zonegran has the longest half-life of the newer AEDs," a claim not based on any head-to-head clinical trials, and which was true only

when Zonegran was used alone, or as monotherapy, an unapproved use.

C. ***Drug T Comparison Flashcard***. In early 2003, **EPI** created a "***Zonegran-Drug T Comparison Flashcard***" to go "head-to-head" with Drug T, which had a broader indication and was well-known to be used for chronic and migraine headaches for which it eventually received approval through an sNDA. The training guide for the sales force explained that: "[t]his hard hitting tool is going to help you take share from Drug T and this primer is going to show you how!" The flashcard contained misleading information regarding the number of patients who had been treated by each drug; misleading claims relating to the similarity in efficacy of the drugs, unsupported claims regarding Zonegran's multiple mechanisms of action, improper claims of differentiation between the drugs and unsupported claims of the superiority of Zonegran. The sales force was told by **EPI** "never" to leave the flashcard behind, and to "use it until they [the FDA] pull it."

D. ***Go Beyond the Max***. Early in 2003, **EPI** targeted Drug T as Zonegran's number one competitor and used a double entendre to get the implied message of superiority across to the physicians. This sales aid also featured people engaging in physical activities that members of the sales force believed were uncommon for patients who suffered from epilepsy, such as snowboarding. The sales aid contained an even more detailed graphic diagram that emphasized the "Multiple Mechanisms of Action" and highlighted qualities of Zonegran that were unrelated to use in epilepsy. The training materials for the sales force indicated, among other messages, that: "ZONEGRAN has also been shown to increase the levels of serotonin in the hippocampus" and that "[r]esearch has shown that the serotonergic and dopaminergic effects of ZONEGRAN are important to physicians who use AEDs for other purposes beyond epilepsy."

EPI's Promotional Techniques to Sell Zonegran for Unapproved Uses

22. At various relevant times, **EPI** promoted Zonegran for uses other than the approved use, including with false and/or misleading claims of safety and efficacy, through the following methods, among others:

A. **EPI** identified physicians who were top priorities for sales calls on "target lists" for the Zonegran sales force. The "target lists" included not only neurologists who treated adults with epilepsy, but also physicians who did not treat epilepsy. At various relevant times, those "target lists" included neurologists who specialized in pediatrics; pain specialists; anesthesiologists; physical rehabilitation specialists; neurologists who specialized in migraines and chronic daily headaches; and child and adult psychiatrists.

B. **EPI** set sales quotas for the Zonegran sales representatives which the representatives were unable to reach unless they actively promoted Zonegran for unapproved uses. Sales bonuses were calculated on the numbers of prescriptions written by doctors for any use of the drug, not just for the approved use, and the sales representatives actively promoted Zonegran for the unapproved uses to obtain sales.

C. **EPI** trained, directed, and encouraged the sales representatives to promote Zonegran for unapproved uses, including among others, pediatric use, pain, psychiatric disorders, chronic headaches/migraines, and movement disorders.

D. **EPI** developed and designed sales aids to assist the sales representatives in promoting Zonegran for unapproved uses through discussions with non-epilepsy doctors. The sales aids were accompanied by training materials called "primers." The primers contained examples of specific dialog to be used by the sales representatives to explain the off-label

meaning of graphic illustrations and diagrams to doctors. The graphic illustrations and diagrams were designed to depict chemical reactions related to non-epilepsy conditions. Through use of the diagrams and sample scripts in the primers, sales representatives led doctors into conversations concerning unapproved uses for Zonegran. Sales representatives routinely used these guides to promote Zonegran for uses other than the approved use of the drug.

E. **EPI** used sham physician requests for medical information about unapproved uses in order to provide unsolicited information to physicians about unapproved uses for Zonegran in the form of "Medical Letters." The sales representatives were encouraged to use, and did use, these medical letters to detail physicians. One particular medical letter used by sales representatives with pediatricians described how to administer Zonegran to a child by putting contents of a Zonegran capsule into applesauce. No mention was made about the fact that the FDA had specifically not approved Zonegran for use in children due to the severe potential side effects of oligohidrosis and hyperthermia.

F. **EPI** provided promotional samples of Zonegran to physicians who EPI knew did not treat epilepsy, including psychiatrists.

G. **EPI** funded purportedly independent continuing medical education programs ("CME") with the purpose of disseminating messages to promote Zonegran for unapproved uses, including specifically for chronic headache, bipolar and acute mania, for children, for obesity and pain. **EPI** hired advertising agencies to prepare standard promotional slides for Zonegran, had the slides certified by other vendors as "CME," and distributed the slides to advocates for use in presentations.

H. **EPI** employed a "robust publication strategy" whereby **EPI** initiated,

funded, sponsored and sometimes drafted or caused articles and presentations to physicians to be ghostwritten about Zonegran for unapproved uses. **EPI** trained the sales force to detail physicians using the publications on unapproved uses.

I. **EPI** conducted "so-called" Advisory Board Meetings for physicians in Bermuda; Key Largo, Florida; Vail, Colorado; Banff, Canada and Tucson, Arizona where potential high prescribers were invited on expense-paid trips to hear speeches on pediatrics, psychiatric disorders including acute mania and bipolar disorder, neuropathic pain, weight loss, pain and chronic headaches.

23. As a result of the sales campaigns and promotional techniques to obtain sales of Zonegran for unapproved uses, the sales of Zonegran increased dramatically. From August 2001 to August 2002, Zonegran prescriptions increased 80.4%; from the 4th quarter 2002 to 4th quarter 2003 Zonegran prescriptions increased 74.1%. Zonegran revenue for the year 2003 was up 87% over 2002 revenue.

COUNT ONE

(Introduction into Interstate Commerce of a Misbranded Drug: 21 U.S.C. §§ 331(a), 333(a)(1) & 352(f)(1))

24. The allegations contained in paragraphs 1 through 23 are realleged and incorporated herein as if set forth in full.

25. Beginning in or about May 2000 and continuing until in or about April 2004, in the District of Massachusetts and elsewhere,

ELAN PHARMACEUTICALS, INC.,

did introduce, deliver for introduction, and cause the introduction into interstate commerce into Massachusetts and elsewhere, quantities of Zonegran, a drug within the meaning of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 321(g), which was intended for use in the treatment of children under the age of 16, neuropathic pain, chronic headaches and migraine headaches, psychiatric disorders including mania and bipolar disorder, movement disorders and as monotherapy for epilepsy and other unapproved uses, which was misbranded within the meaning of 21 U.S.C. § 352(f)(1), in that its labeling lacked adequate directions for such uses.

All in violation of 21 U.S.C. §§ 331(a), 333(a)(1), and 352(f)(1).

FORFEITURE ALLEGATIONS

1. Upon conviction of any violation of Title 21, United States Code, Sections 331(a), 333(a)(1), and 352(f)(l) set forth in this information, defendant,

ELAN PHARMACEUTICALS, INC.

shall forfeit to the United States of America pursuant to Title 21, United States Code, Section 334 and Title 28, United States Code, Section 2461(c), any quantities of Zonegran, which were introduced into interstate commerce in violation of Title 21, United States Code, Section 331.

2. If any of the property subject to forfeiture, as a result of any act or omission of the defendant:

(a) cannot be located upon the exercise of due diligence;

(b) has been transferred or sold to, or deposited with, a third party;

(c) has been placed beyond the jurisdiction of the Court;

(d) has been substantially diminished in value; or

(e) has been commingled with other property which cannot be divided without difficulty;

it is the intent of the United States, pursuant to Title 28, United States Code, Section 2461(c), incorporating Title 21, United States Code, Section 853(p), to seek forfeiture of any other property of the defendant up to the value of the property subject to forfeiture, that is $3,600,000 in United States currency.

All pursuant to Title 21, United States Code, Sections 334 and 853 and Title 28, United States Code, Section 246l(c).

CARMEN M. ORTIZ
UNITED STATES ATTORNEY
DISTRICT OF MASSACHUSETTS

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